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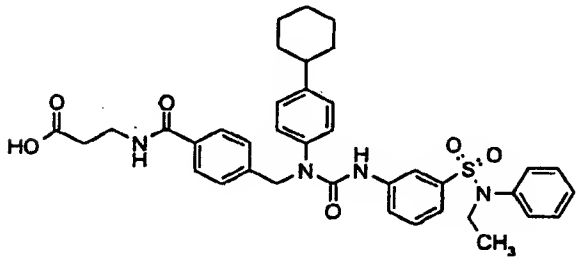
(54) Title: GLUCAGON ANTAGONISTS/INVERSE AGONISTS

(57) Abstract

A novel class of compounds, which act to antagonize the action of the glucagon hormone on the glucagon receptor. Owing to their antagonizing effect of the glucagon receptor the compounds may be suitable for the treatment and/or prevention of any glucagon–mediated conditions and diseases such as hyperglycemia, Type 1 diabetes, Type 2 diabetes and obesity.

EXAMPLE 265 (gen ral procedure (L))

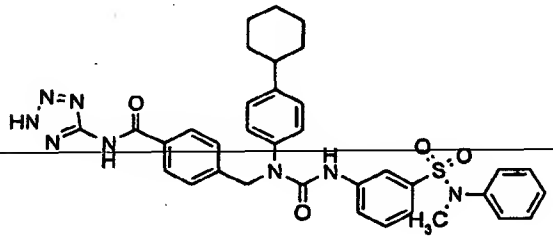
3-(4-{1-(4-Cyclohexylphenyl)-3-[3-(ethylphenylsulfamoyl)phenyl]ureidomethyl}benzoylamino)-propionic acid



HPLC-MS (Method B): m/z = 683 (M+1). R_t = 7.60 min.

EXAMPLE 266 (general procedure (L))

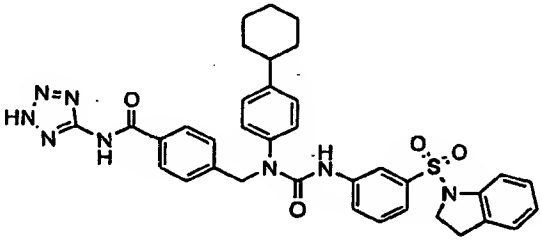
4-{1-(4-Cyclohexylphenyl)-3-[3-(methylphenylsulfamoyl)phenyl]ureidomethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method B): m/z = 665 (M+1). R_t = 7.67 min.

EXAMPLE 267 (general procedure (L))

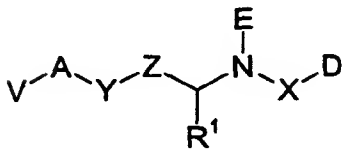
4-{1-(4-Cyclohexylphenyl)-3-[3-(2,3-dihydroindole-1-sulfonyl)phenyl]ureidomethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method B): m/z = 677 (M+1). R_t = 7.75 min.

CLAIMS

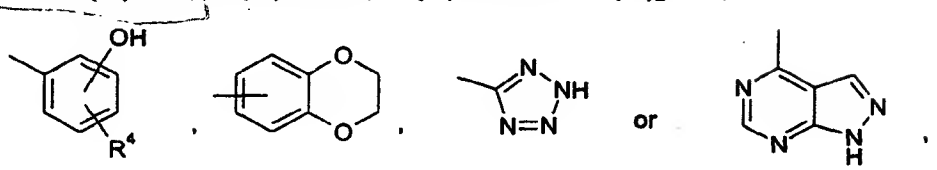
1. A compound of the general formula (I):



(I)

wherein

V is $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NR^2OR^3$, $-S(O)_2OR^2$,



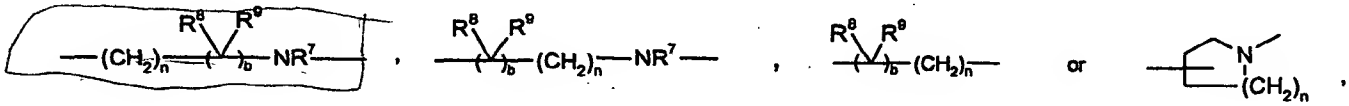
wherein

R^2 and R^3 independently are hydrogen or C_{1-6}-alkyl,

R^4 is hydrogen, halogen, -CN, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^5$, $-NR^5R^6$ or C_{1-6}-alkyl,

wherein R^5 and R^6 independently are hydrogen or C_{1-6}-alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6}-alkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

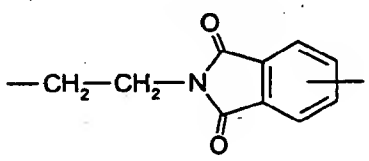
Y is -C(O)-, -$S(O)_2$-, -O- or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^{46} and R^{47} selected from hydrogen, halogen, -CN, -CF_3, -OCF_3, -NO_2, -OR^{10}, -$NR^{10}R^{11}$ and C_{1-6}-alkyl,

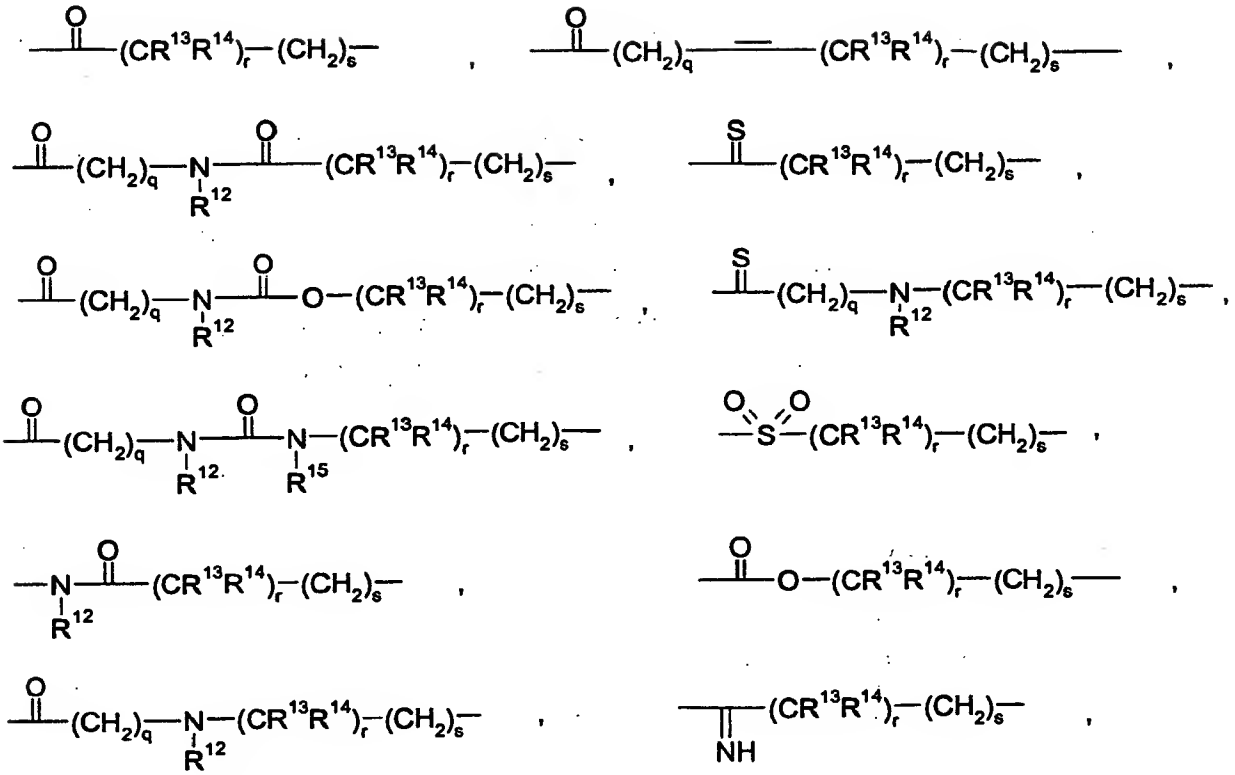
wherein R^{10} and R^{11} independently are hydrogen or C_{1-6}-alkyl,

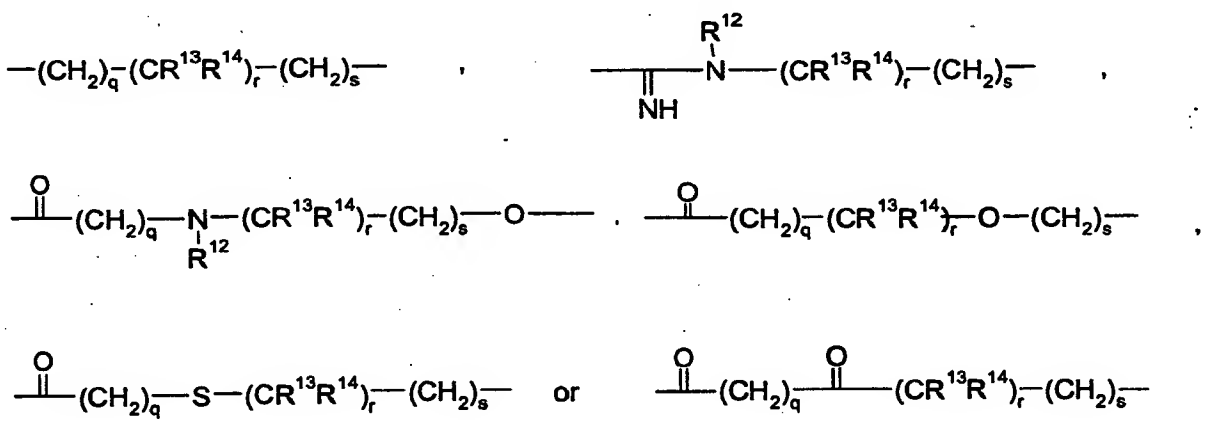
or -A-Y-Z- together are



R^1 is hydrogen or C_{1-6}-alkyl,

X is





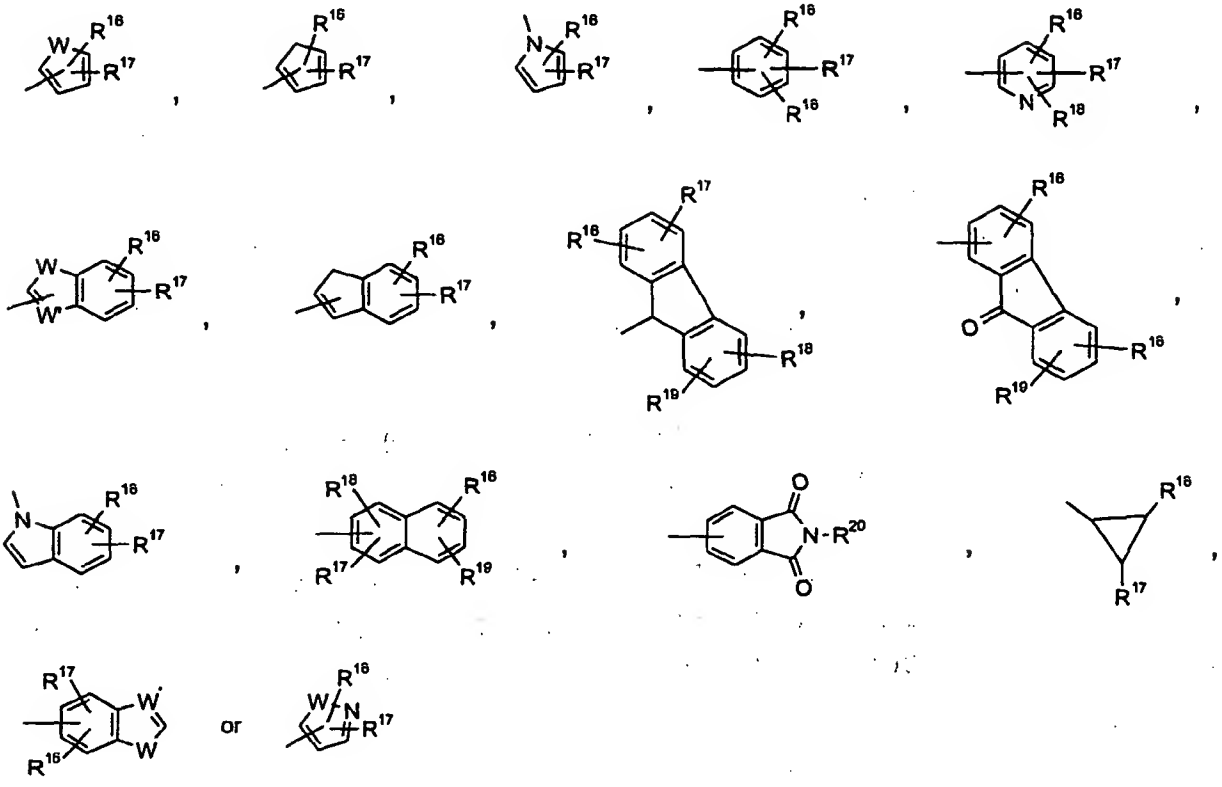
wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{12}, R^{13}, R^{14} and R^{15} independently are hydrogen or C_{1-6}-alkyl,

D is



wherein

W is -O-, -S-, -$S(O)_2$- or -NR^{20}-,

W' is =$CR^{20'}$- or =N-,

R^{16}, R^{17}, R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$OS(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$C(O)R^{21}$ or -$C(O)OR^{21}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

- C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyloxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio, C_{3-8}-cycloalkylthio, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-8}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl or heterocyclyl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from

  -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

  C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents select d from

halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$NR^{21}S(O)_2R^{22}$, -$S(O)_2NR^{21}R^{22}$, -$S(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$OS(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$CH_2C(O)NR^{21}R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -CH_2OR^{21}, -$CH_2NR^{21}R^{22}$, -$OC(O)R^{21}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{21}, -$NR^{21}R^{22}$, -SR^{21}, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$C(O)NR^{21}R^{22}$, -$OC(O)NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OCH_2C(O)NR^{21}R^{22}$, -$C(O)R^{21}$ and -$C(O)OR^{21}$,

wherein R^{21} and R^{22} independently are hydrogen, -CF_3, C_{1-6}-alkyl, tri-C_{1-6}-alkylsilyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, aryl, aryl-C_{1-6}-alkyl or heteroaryl,

or R^{21} and R^{22} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{16} to R^{19} when placed in adjacent positions together may form a bridge –$(CR^{16'}R^{17'})_a$-O-$(CR^{18'}R^{19'})_c$-O-,

wherein

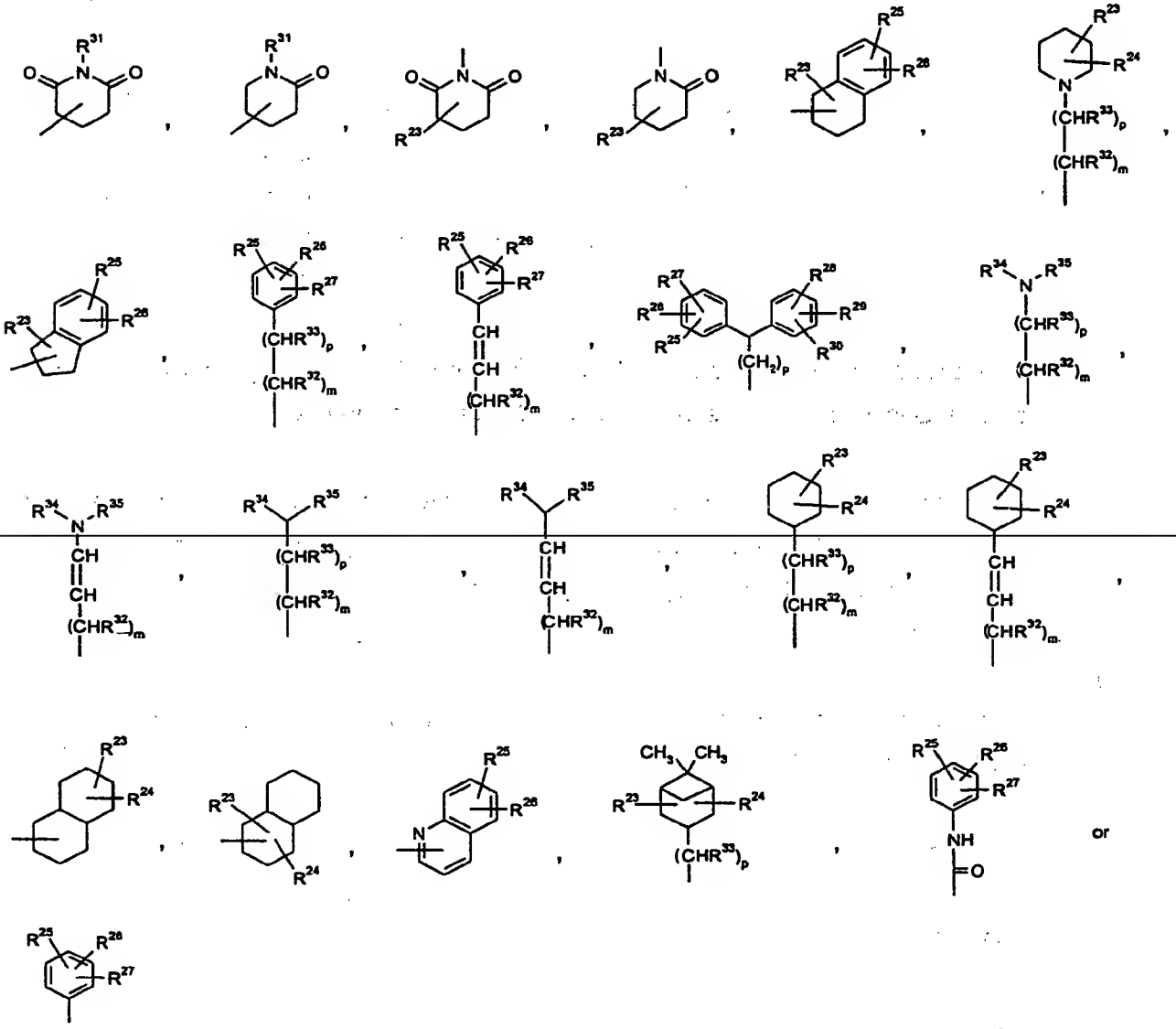
a is 0, 1 or 2,

c is 1 or 2,

$R^{16'}$, $R^{17'}$, $R^{18'}$ and $R^{19'}$ independently are hydrogen, C_{1-6}-alkyl or halogen,

R^{20} and $R^{20'}$ independently are hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom when present, or



wherein

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the sam formula at least one of m and p is different from 0,

R^{23} and R^{24} independently are

- hydrogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{38}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ or $-C(O)OR^{36}$,

- C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{38}$ and $-C(O)OR^{36}$,

- C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylidene, C_{4-8}-cycloalkenyl, heterocyclyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl, C_{4-8}-cycloalkenyl-C_{1-6}-alkyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkenyl, C_{4-8}-cycloalkenyl-C_{2-6}-alkynyl, heterocyclyl-C_{1-6}-alkyl, heterocyclyl-C_{2-6}-alkenyl or heterocyclyl-C_{2-6}-alkynyl,

  of which the cyclic moieties optionally may be substituted with one or more substituents selected from

  $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

  C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{36}$, $-NR^{36}R^{37}$, $-SR^{36}$, $-S(O)R^{36}$, $-S(O)_2R^{36}$, $-C(O)NR^{36}R^{37}$, $-OC(O)NR^{36}R^{37}$, $-NR^{36}C(O)R^{37}$, $-OCH_2C(O)NR^{36}R^{37}$, $-C(O)R^{36}$ and $-C(O)OR^{36}$,

- aryl, aryloxy, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl, heteroaryl-C_{1-6}-alkyl, heteroaryl-C_{2-6}-alkenyl or heteroaryl-C_{2-6}-alkynyl,

  of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

  halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^{36}, -$NR^{36}R^{37}$, -SR^{36}, -$NR^{36}S(O)_2R^{37}$, -$S(O)_2NR^{36}R^{37}$, -$S(O)NR^{36}R^{37}$, -$S(O)R^{36}$, -$S(O)_2R^{36}$, -$OS(O)_2R^{36}$, -$C(O)NR^{36}R^{37}$, -$OC(O)NR^{36}R^{37}$, -$NR^{36}C(O)R^{37}$, -$CH_2C(O)NR^{36}R^{37}$, -$CH_2C(O)NR^{36}R^{37}$, -CH_2OR^{36}, -$CH_2NR^{36}R^{37}$, -$OC(O)R^{36}$, -$C(O)R^{36}$ and -$C(O)OR^{36}$,

  C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl,

  which may optionally be substituted with one or more substituents selected from -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -SCF_3, -OR^{36}, -$NR^{36}R^{37}$, -SR^{36}, -$S(O)R^{36}$, -$S(O)_2R^{36}$, -$C(O)NR^{36}R^{37}$, -$OC(O)NR^{36}R^{37}$, -$NR^{36}C(O)R^{37}$, -$OCH_2C(O)NR^{36}R^{37}$, -$C(O)R^{36}$ and -$C(O)OR^{36}$,

wherein R^{36} and R^{37} independently are hydrogen, C_{1-6}-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -NO_2, -OR^{38}, -$NR^{38}R^{39}$ and C_{1-6}-alkyl,

wherein R^{36} and R^{39} independently are hydrogen or C_{1-6}-alkyl,

or R^{36} and R^{37} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R^{23} and R^{24} when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-$(CH_2)_t$-$CR^{40}R^{41}$-$(CH_2)_r$-O-, -$(CH_2)_t$-$CR^{40}R^{41}$-$(CH_2)_r$- or

$-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

R^{40} and R^{41} independently are hydrogen or C_{1-6}-alkyl,

R^{25} to R^{30} independently are hydrogen, halogen, -CN, $-CF_3$, $-NO_2$, $-OR^{42}$, $-NR^{42}R^{43}$, C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{4-8}-cycloalkenyl,

wherein R^{42} and R^{43} independently are hydrogen or C_{1-6}-alkyl, or

R^{42} and R^{43} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R^{31}, R^{32} and R^{33} independently are hydrogen or C_{1-6}-alkyl,

R^{34} and R^{35} independently are

- hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkanoyl, $-C(O)NR^{44}R^{45}$ or $-S(O)_2R^{45}$,
- aryl, aroyl, aryl-C_{1-6}-alkoxy, aryl-C_{1-6}-alkanoyl or aryl-C_{1-6}-alkyl,

  of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, $-CF_3$, $-OCF_3$, $-OR^{44}$, $-NR^{44}R^{45}$ and C_{1-6}-alkyl,

wherein R^{44} and R^{45} independently are hydrogen or C_{1-6}-alkyl, or

R^{34} and R^{35} when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing on or two double bonds, or

R^{34} and R^{35} when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

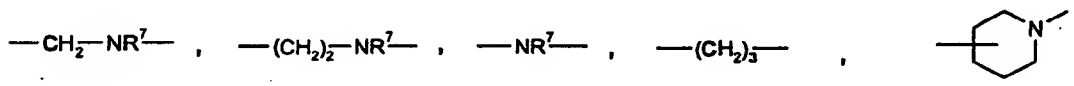
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein V is -C(O)OH, -$S(O)_2$OH, -C(O)NHOH or 5-tetrazolyl.

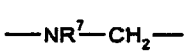
3. A compound according to claim 2, wherein V is -C(O)OH.

4. A compound according to claim 2, wherein V is 5-tetrazolyl.

5. A compound according to any one of the claims 1 to 4, wherein A is

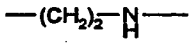


or

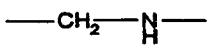


wherein R^7 is as defined in claim 1.

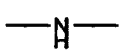
6. A compound according to claim 5, wherein A is



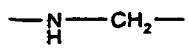
7. A compound according to claim 5, wherein A is



8. A compound according to claim 5, wherein A is



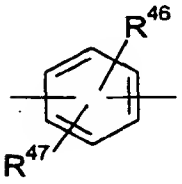
9. A compound according to claim 5, wherein A is



10. A compound according to any one of the claims 1 to 9, wherein Y is -C(O)-.

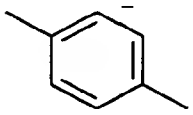
11. A compound according to any one of the claims 1 to 9, wherein Y is a valence bond.

12. A compound according to any one of the claims 1 to 11, wherein Z is



wherein R^{46} and R^{47} are as defined in claim 1.

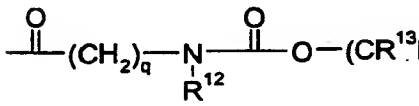
13. A compound according to claim 12, wherein Z is



14. A compound according to any one of the claims 1 to 13, wherein R^1 is hydrogen.

15. A compound according to any one of the claims 1 to 13, wherein R^1 is methyl.

16. A compound according to any one of the claims 1 to 15, wherein X is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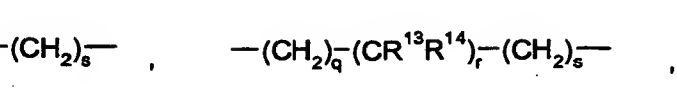
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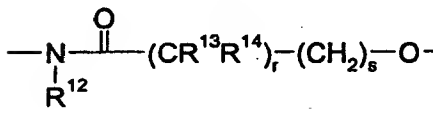
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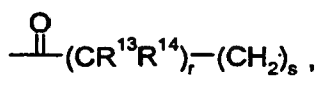
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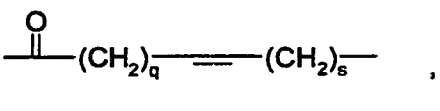
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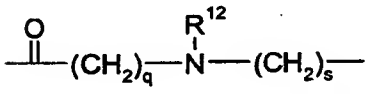
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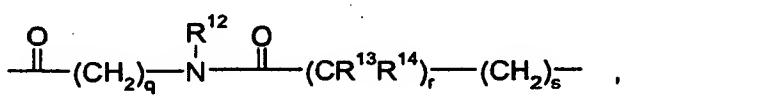
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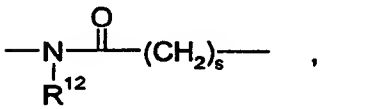
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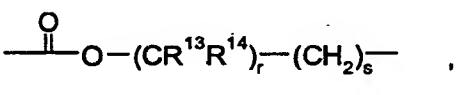
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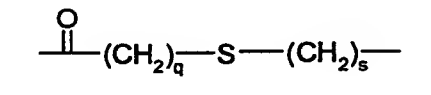
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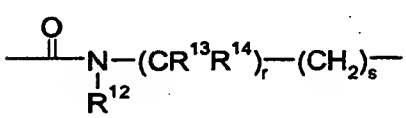
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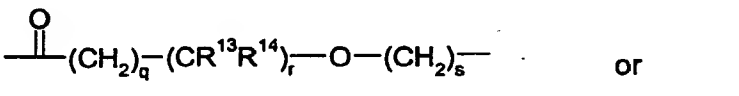
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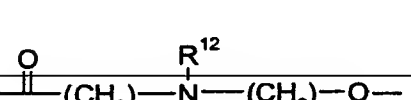
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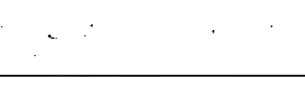
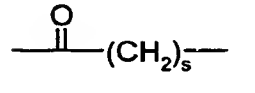

or

,

wherein q, r, s, R^{12}, R^{13} and R^{14} are as defined in claim 1.

17. A compound according to claim 16, wherein X is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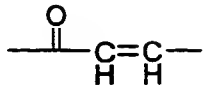
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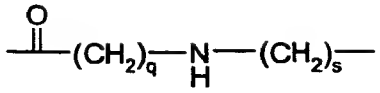
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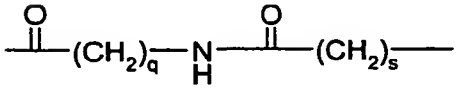
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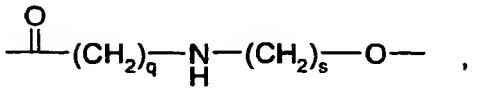
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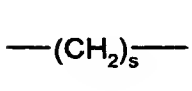
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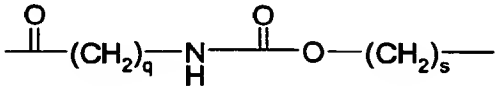
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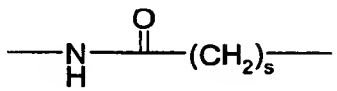
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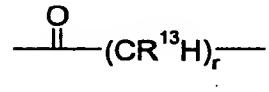
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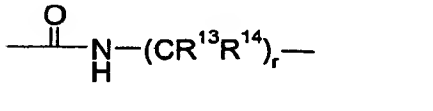
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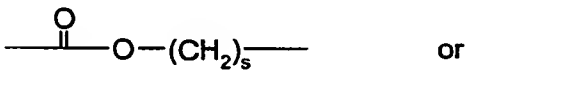

or

wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R^{13} is hydrogen or C_{1-6}-alkyl.

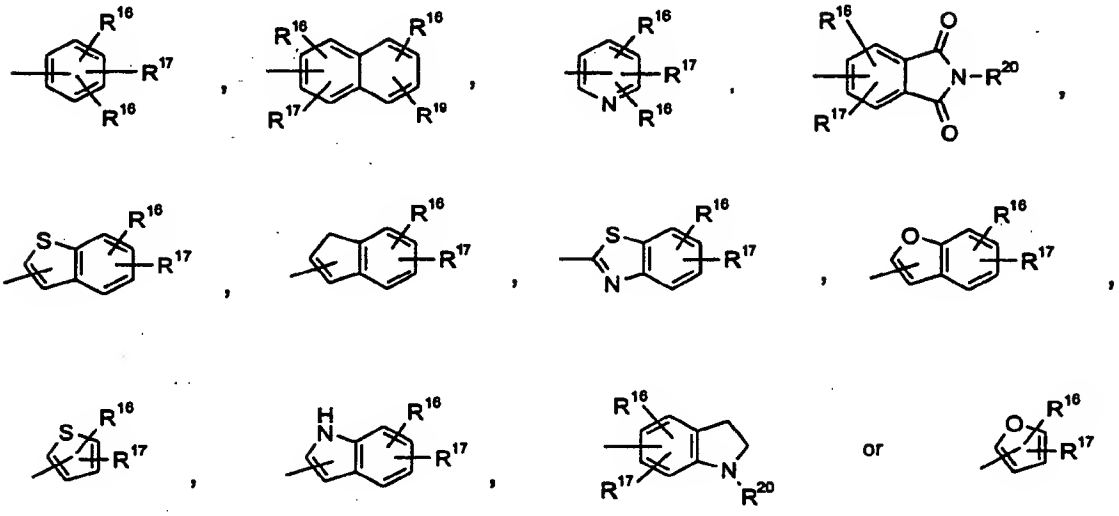
18. A compound according to claim 17, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -C(O)CH=CH-, -(CH$_2$)$_s$-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

19. A compound according to claim 18, wherein X is -C(O)NH-, -C(O)NHCH$_2$-, -C(O)NHCH(CH$_3$)-, -C(O)NHCH$_2$CH$_2$-, -C(O)CH$_2$-, -CH$_2$-, -C(O)- or -NHC(O)-.

20. A compound according to claim 19, wherein X is -C(O)NH-.

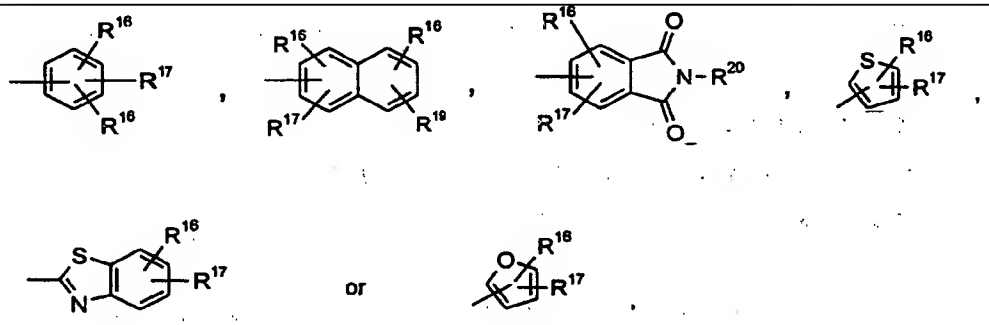
21. A compound according to claim 19, wherein X is -C(O)NHCH(CH$_3$)-.

22. A compound according to any one of the claims 1 to 21, wherein D is



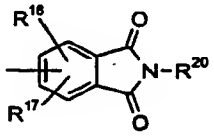
wherein R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are as defined in claim 1.

23. A compound according to claim 22, wherein D is



wherein R^{16}, R^{17}, R^{18} and R^{20} are as defined in claim 1.

24. A compound according to claim 23, wherein D is



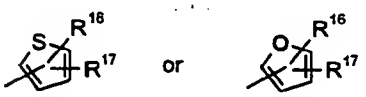
wherein R^{16}, R^{17} and R^{20} are as defined in claim 1.

25. A compound according to claim 24, wherein R^{16} and R^{17} are both hydrogen and R^{20} is C_{1-6}-alkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl.

26. A compound according to claim 24 or 25, wherein R^{20} is cyclopropylmethyl, butyl or isopropyl.

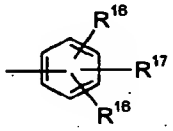
27. A compound according to claim 26, wherein R^{20} is isopropyl.

28. A compound according to claim 23, wherein D is



wherein R^{16} and R^{17} are as defined in claim 1.

29. A compound according to claim 23, wherein D is



wherein R^{16}, R^{17} and R^{16} are as defined in claim 1.

30. A compound according to any one of the claims 22, 23, 28 or 29, wherein R^{16}, R^{17} and R^{18} independently are

hydrogen, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, hydroxy, $-SCF_3$, C_{1-6}-alkyl, C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkyl substituted with $-S(O)_2R^{21}$, C_{1-6}-alkoxy, $-S-C_{1-6}$-alkyl, $-C(O)OR^{21}$, $-C(O)R^{21}$, $-CH_2(O)R^{21}$, $-C(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-S(O)_2CF_3$, $-S(O)_2NR^{21}R^{22}$, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio or C_{3-8}-cycloalkylthio,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl, tri-C_{1-6}-alkylsilyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl, phenyl-C_{1-6}-alkyl, 2,3-dihydroindolyl or isoindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

phenoxy, phenoxycarbonyl, phenyl, phenyl-C_{1-6}-alkoxy, phenyl-C_{1-6}-alkyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF_3, -OCF_3, -NO_2, -$C(O)OR^{21}$, -OR^{21}, -$NR^{21}R^{22}$ or C_{1-6}-alkyl, wherein R^{21} and R^{22} independently are hydrogen or C_{1-6}-alkyl, or

wherein R^{16} and R^{17} in adjacent positions form the radical -O-CH_2-O-, -CF_2-O-CF_2-O- or -O-CF_2-CF_2-O-, and R^{18} is hydrogen.

31. A compound according to claim 30, wherein R^{16}, R^{17} and R^{18} independently are

hydrogen, halogen, -CN, -NO_2, -CF_3, -OCF_3, -SCF_3, C_{1-6}-alkyl, C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkyl substituted with -$S(O)_2R^{21}$, C_{1-6}-alkoxy, -S-C_{1-6}-alkyl, -$C(O)OR^{21}$, -$C(O)R^{21}$, -$CH_2(O)R^{21}$, -$C(O)NR^{21}R^{22}$, -$S(O)R^{21}$, -$S(O)_2R^{21}$, -$S(O)_2CF_3$, -$S(O)_2NR^{21}R^{22}$, C_{3-8}-cycloalkyl-C_{1-6}-alkoxy, C_{3-8}-cycloalkyl-C_{1-6}-alkylthio or C_{3-8}-cycloalkylthio,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl, tri-C_{1-6}-alkylsilyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, phenyl or 2,3-dihydroindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -$C(O)OR^{21}$ or C_{1-6}-alkyl, wherein R^{21} is hydrogen or C_{1-6}-alkyl, or

wherein R^{18} and R^{17} in adjacent positions form the radical -CF_2-O-CF_2-O- or -O-CF_2-CF_2-O-, and R^{18} is hydrogen.

32. A compound according to claim 31, wherein R^{16}, R^{17} and R^{18} independently are

hydrogen, halogen, -CN, -NO_2, -CF_3, -OCF_3, -SCF_3, C_{1-6}-alkyl, C_{1-6}-alkyl substituted with hydroxy, C_{1-6}-alkoxy, -S-C_{1-6}-alkyl, -$C(O)OR^{21}$, -$C(O)R^{21}$, -$CH_2(O)R^{21}$, -$C(O)NR^{21}R^{22}$, -$S(O)_2R^{21}$, -$(O)_2CF_3$ or -$S(O)_2NR^{21}R^{22}$,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6}-alkyl, tri-C_{1-6}-alkylsilyl, phenyl or 2,3-dihydroindolyl,

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -C(O)OR^{21} or C_{1-6}-alkyl, wherein R^{21} is hydrogen or C_{1-6}-alkyl, or

wherein R^{18} and R^{17} in adjacent positions form the radical -CF_2-O-CF_2-O- or -O-CF_2-CF_2-O-, and R^{16} is hydrogen.

33. A compound according to claim 32, wherein R^{16}, R^{17} and R^{18} independently are hydrogen, halogen, -CN, -NO_2, -CF_3, -OCF_3, -SCF_3, C_{1-6}-alkyl, C_{1-6}-alkoxy, -S-C_{1-6}-alkyl, -C(O)OC_{1-6}-alkyl, -S(O)$_2$$C_{1-6}$-alkyl , -S(O)$_2$$CF_3$, -C(O)N($C_{1-6}$-alkyl)($C_{1-6}$-alkyl), -S(O)$_2$N(phenyl)($C_{1-6}$-alkyl), -C(=O)$C_{1-6}$-alkyl, -$CH_2$OH, -$CH_2$O(tri-$C_{1-6}$-alkylsilyl), 2,3-dihydroindol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-yl).

34. A compound according to any one of the claims 30 to 33, wherein one of R^{16} to R^{18} is hydrogen.

35. A compound according to any one of the claims 30 to 33, wherein two of R^{16} to R^{18} are hydrogen.

36. A compound according to claim 30, wherein R^{18} and R^{17} are both hydrogen and R^{18} is -OCF_3, -SCF_3 -CF_3, –S(O)$_2$$CH_3$, phenyl, halogen, C_{1-6}-alkyl, nitro, -S-C_{1-6}-alkyl or -S(O)$_2$NR^{21}R^{22}, wherein R^{21} is C_{1-6}-alkyl and R^{22} is phenyl.

37. A compound according to claim 30, wherein R^{16} and R^{17} are both hydrogen and R^{18} is -OCF_3 or halogen.

38. A compound according to claim 30, wherein R^{16} is hydrogen and R^{17} and R^{18} are both halogen or are both –CF_3.

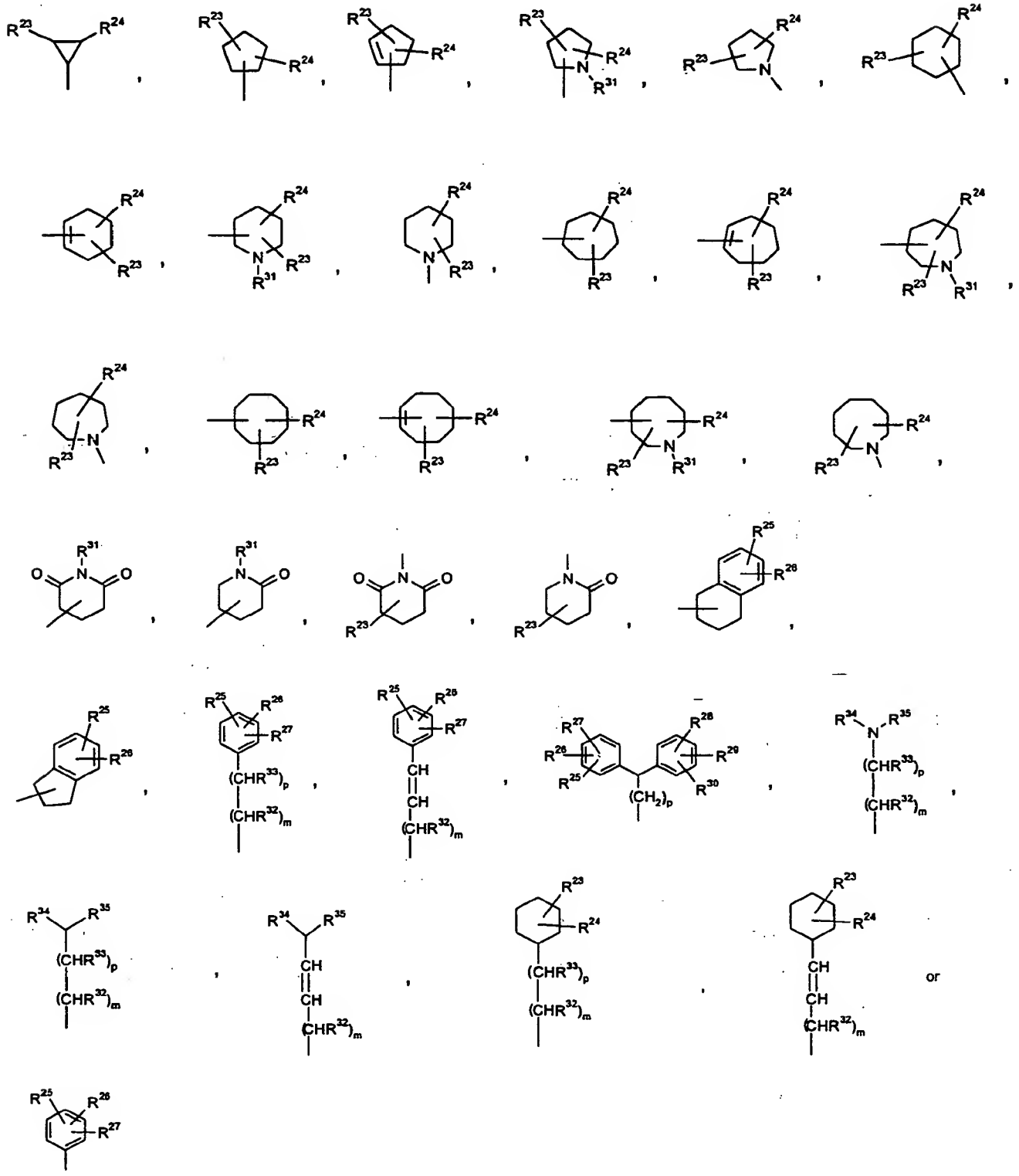
39. A compound according to claim 30, wherein R^{16} is hydrogen, R^{17} is –CF_3 and R^{18} is halogen, -CN, C_{1-6}-alkoxy or –OCF_3.

40. A compound according to claim 30, wherein R^{16} is hydrogen, R^{17} is $-OCF_3$ and R^{18} is $-S(O)_2CH_3$, $-CH_2O$-tri-C_{1-6}-alkylsilyl, benzoxazolyl or $-CH_2OH$.

41. A compound according to claim 30, wherein R^{16} is hydrogen, R^{17} is C_{1-6}-alkyl and R^{18} is $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6}-alkyl and R^{22} is phenyl.

42. A compound according to claim 30, wherein R^{16}, R^{17} and R^{18} are selected from hydrogen, $-OCF_3$, $-CF_3$, -Br, -F and –Cl.

43. A compound according to any one of the preceding claims, wher in E is

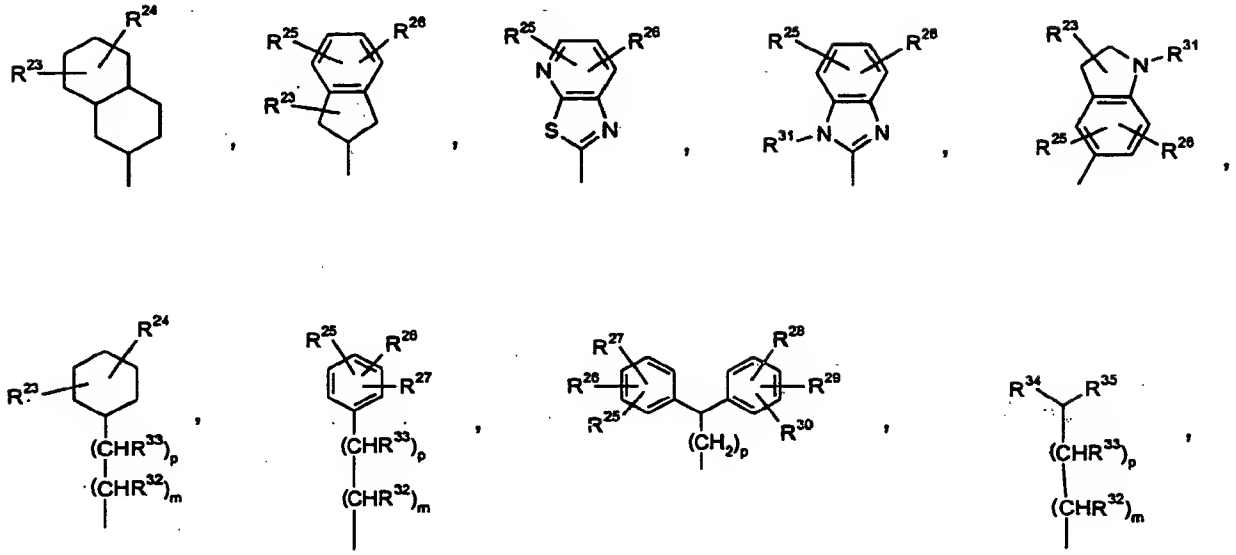


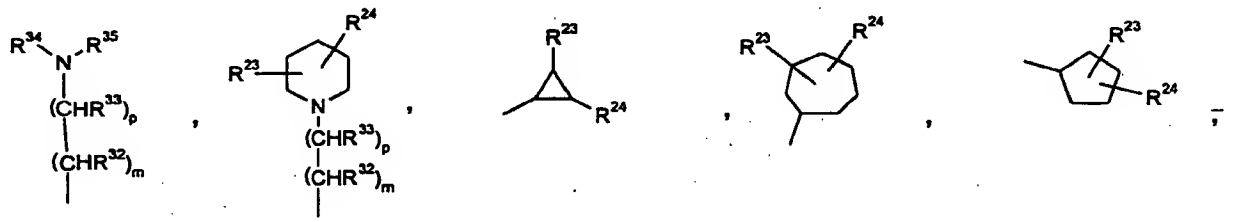
or

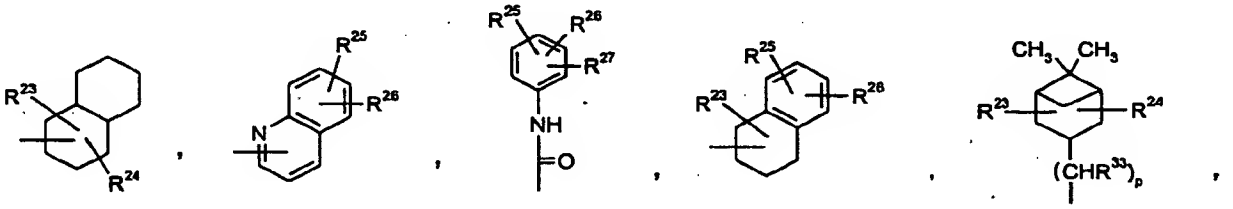
wherein

m, p and R^{23} to R^{35} are as defined in claim 1.

44. A compound according to claim 43, wherein E is

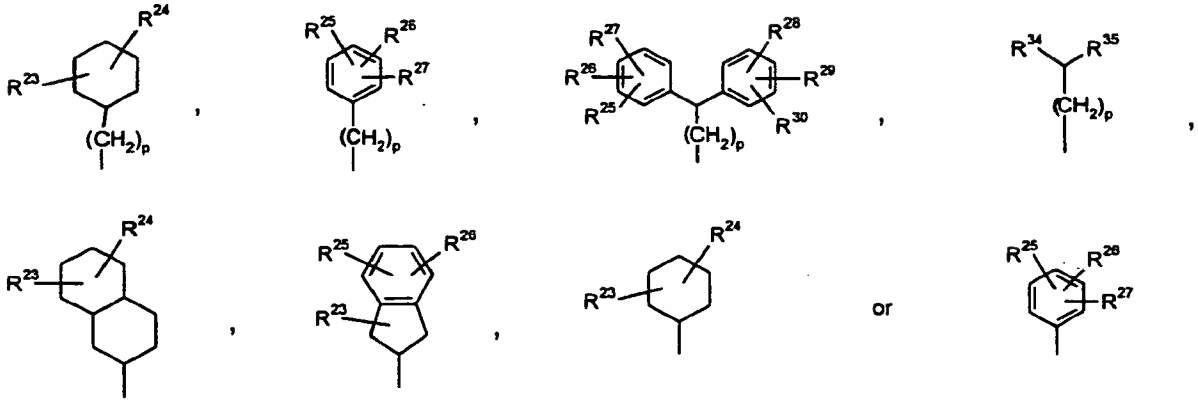






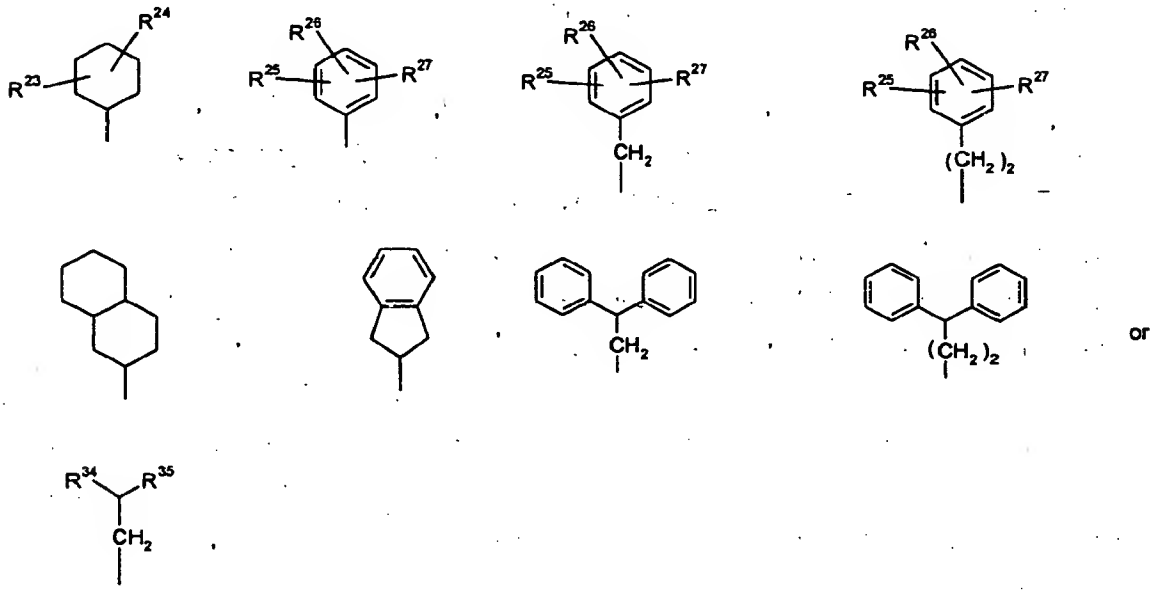
wherein m, p and R^{23} to R^{35} are as defined in claim 1.

45. A compound according to claim 44, wherein E is



wherein p, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{34} and R^{35} are as defined in claim 1.

46. A compound according to claim 45, wherein E is

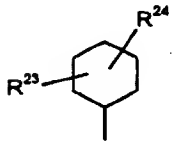


wherein R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{34} and R^{35} are as defined in claim 1.

47. A compound according to claim 46, wherein R^{34} and R^{35} independently are C_{1-6}-alkyl, hydrogen or C_{1-6}-alkoxy.

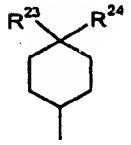
48. A compound according to claim 47, wherein R^{34} and R^{35} are both C_{1-6}-alkyl.

49. A compound according to claim 45, wherein E is



wherein R^{23} and R^{24} are as defined in claim 1.

50. A compound according to claim 49, wherein E is

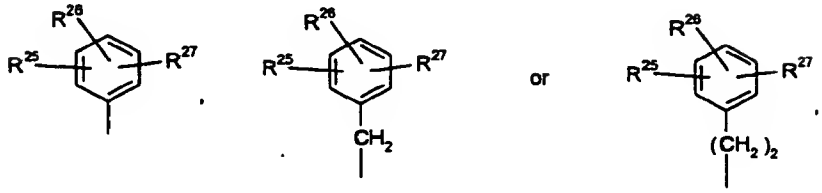


wherein R^{23} and R^{24} are as defined in claim 1.

51. A compound according to claim 49 or 50, wherein R^{23} and R^{24} independently are selected from hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkylidene, phenoxy, phenyl, $-C(O)NR^{36}R^{37}$ and -OC(O)NH-phenyl, of which the phenyl moiety optionally may be substituted with $-OCF_3$, wherein R^{36} and R^{37} are as defined in claim 1, or R^{23} and R^{24} together form the radical $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$, $-O-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-O-$, $-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$, wherein t, l, R^{40} and R^{41} are as defined in claim 1.

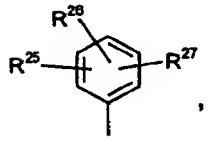
52. A compound according to claim 51, wherein R^{23} is hydrogen and R^{24} is C_{1-6}-alkyl such as *tert*-butyl or C_{3-8}-cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C_{1-6}-alkyl or wherein R^{23} and R^{24} together form the radical $-(CH_2)_5-$.

53. A compound according to claim 46, wherein E is



wherein R^{25}, R^{26} and R^{27} are as defined in claim 1.

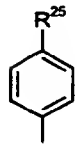
54. A compound according to claim 53, wherein E is



wherein R^{25}, R^{26} and R^{27} are as defined in claim 1.

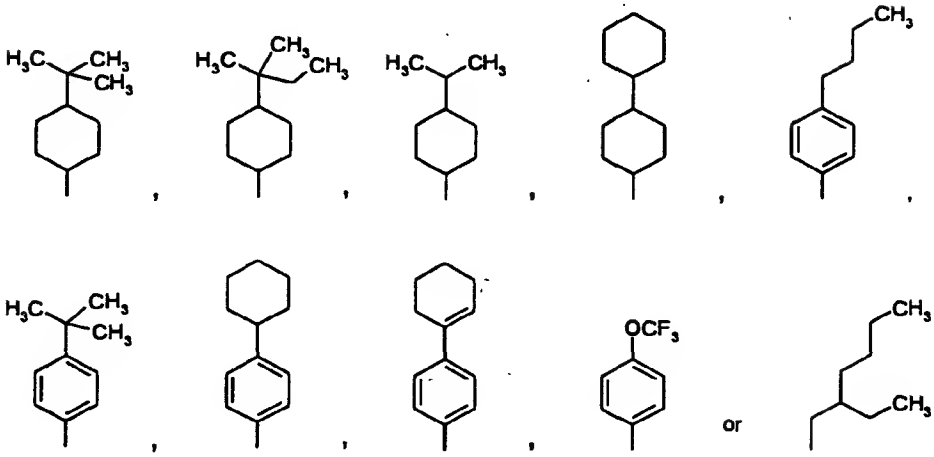
55. A compound according to claim 53 or 54, wherein R^{25}, R^{26} and R^{27} independently are selected from hydrogen, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-8}-cycloalkyl, C_{4-8}-cycloalkenyl, $-CF_3$, $-OCF_3$ or $-NR^{42}R^{43}$, wherein R^{42} and R^{43} are as defined in claim 1.

56. A compound according to claim 55, wherein E is

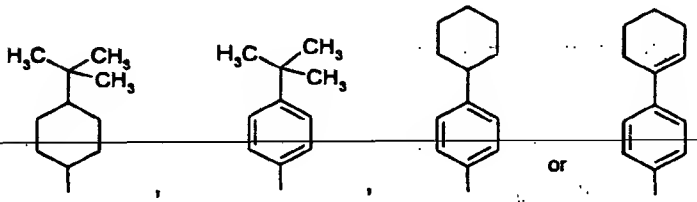


wherein R^{25} is $-OCF_3$, $-CF_3$, C_{1-6}-alkyl such as *tert*-butyl, piperidyl, C_{3-8}-cycloalkyl such as cyclohexyl or C_{4-8}-cycloalkenyl such as cyclohexenyl.

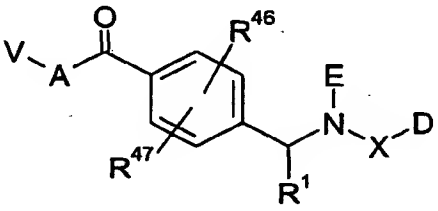
57. A compound according to claim 46, wherein E is



58. A compound according to claim 57, wherein E is



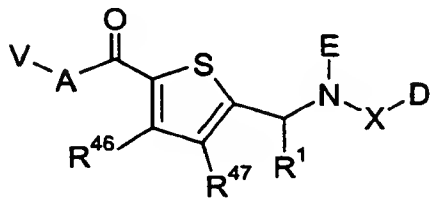
59. A compound according to claim 1 of the general formula (I_1):



(I_1)

wherein V, A, R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

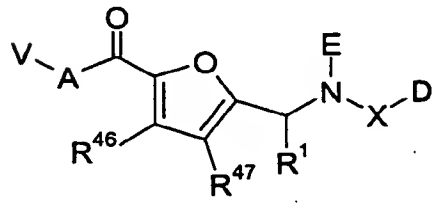
60. A compound according to claim 1 of the general formula (I_2):



(I_2)

wherein V, A, R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

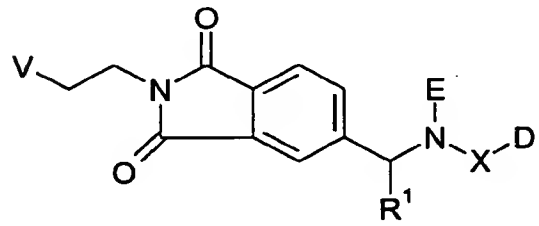
61. A compound according to claim 1 of the general formula (I_3):



(I_3)

wherein V, A, R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

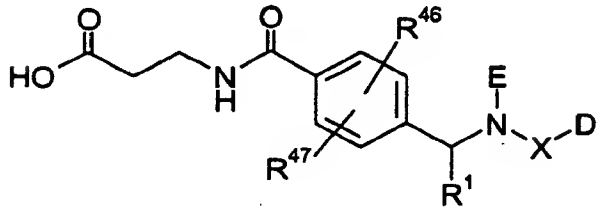
62. A compound according to claim 1 of the general formula (I_4):



(I_4)

wherein V is $-C(O)OR^2$, $-C(O)NR^2R^3$ or $-C(O)NR^2OR^3$, and R^1, R^2, R^3, E, X and D are as defined in claim 1 or in any one of the preceding claims.

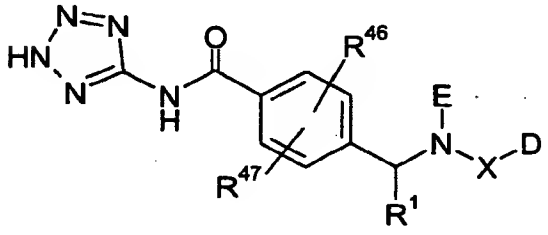
63. A compound according to claim 1 of the general formula (I_5):



(I_5)

wherein R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

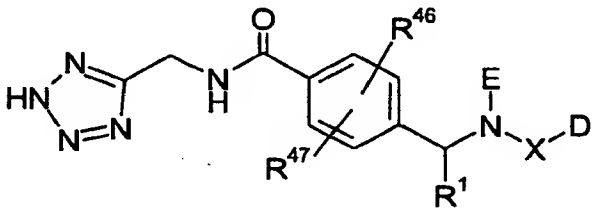
64. A compound according to claim 1 of the general formula (I_6):



(I_6)

wherein R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

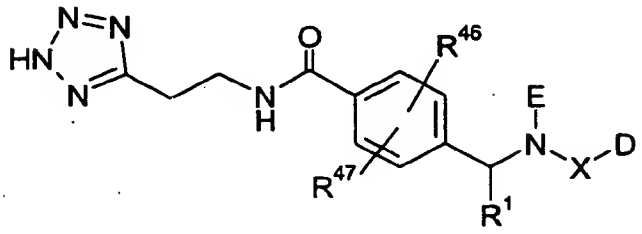
65. A compound according to claim 1 of the general formula (I_7):



(I_7)

wherein R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

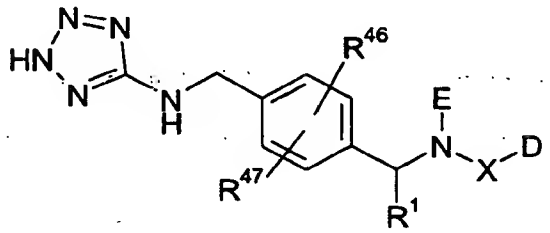
66. A compound according to claim 1 of the general formula (I_8):



(I_8)

wherein R^{46}, R^{47}, R^1, E, X and D are as defined in claim1 or in any one of the preceding claims.

67. A compound according to claim 1 of the general formula (I_9):



(I_9)

wherein R^{46}, R^{47}, R^1, E, X and D are as defined in claim 1 or in any one of the preceding claims.

68. A compound according to anyone of the claims 59 to 61 or 63 to 67, wherein R^{46} and R^{47} are both hydrogen.

69. A compound according to any one of the preceding claims, which has an IC_{50} value of no greater than 5 μM as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein.

70. A compound according to claim 69 characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclos d herein corresponding to an IC_{50} value of less than 1 μM, preferably of less than 500 nM and even more preferred of less than 100 nM.

71. A compound according to any one of the preceding claims, which is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT, Type 2 diabetes, Type 1 diab tes and obesity.

72. A compound according to any one of the claims 1 to 71 for use as a medicament.

73. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 71 together with one or more pharmaceutically acceptable carriers or excipients.

74. A pharmaceutical composition according to claim 73 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 71.

75. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

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76. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

77. Use of a compound according to any one of the claims 1 to 71 for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

78. Use of a compound according to any one of the claims 1 to 71 for the manufacture of a medicament for lowering blood glucose in a mammal.

79. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of IGT.

80. Use of a compound according to any one of the claims 1 to 71 for the preparation of a m dicament for the treatment and/or prevention of Type 2 diab tes.

81. Use according to claim 80 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

82. Use according to claim 80 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

83. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

84. Use according to any one of the claims 75 to 83 in a regimen which additionally comprises treatment with another antidiabetic agent.

85. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of obesity.

86. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of obesity in a regimen which additionally comprises treatment with another antiobesity agent.

87. A method for the treatment and/or prevention of disorders or diseases mediated by a glucagon antagonistic action, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 71 or a pharmaceutical composition according to claim 73 or 74.

88. The method according to claim 87, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00264

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 237/32, C07C 243/24, C07C 271/40, C07C 275/28, C07D 209/48, C07D 257/04, C07D 333/04, A61K 31/15, A61K 31/165, A61K31/17, A61K 31/33, A61P 3/04, A61P 3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9901423 A1 (NOVO NORDISK A/S ET AL), 14 January 1999 (14.01.99) --	1-88
A	EP 0847992 A1 (MITSUI CHEMICALS, INC.), 17 June 1998 (17.06.98) --	1-88
A	EP 0000816 A1 (BEECHAM GROUP LIMITED), 21 February 1979 (21.02.79) -- --------	1-88

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 Sept 2000	27 -09- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00264

B x I Observations where certain claims were found unsearchable (Continuation f item 1 f first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 87-88
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet*

2. ☒ Claims Nos.: 1-58, 69-88
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*Claims 87-88 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv).
Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compound(s)/composition(s).

**Present claims 1-58 and 69-88 relate to an extremely large number of possible compounds. In fact, the claims contains so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, a limited search has been carried out on the basis of claims 59-68.

Claim 5 (when A = -NR7-CH2-) and claim 9 (A = -NH-CH2-) do not seem to be depending on claim 1.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/08/00

International application No.
PCT/DK 00/00264

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9901423 A1	14/01/99	AU 7908398 A	25/01/99
		EP 0994848 A	26/04/00
		NO 996550 A	29/02/00
		ZA 9805759 A	25/01/99
EP 0847992 A1	17/06/98	JP 10152462 A	09/06/98
EP 0000816 A1	21/02/79	AU 3862078 A	07/02/80
		DK 346278 A	07/02/79
		ES 472384 A	01/10/79
		ES 479931 A	01/12/79
		ES 479932 A	01/12/79
		ES 479933 A	01/12/79
		IL 55242 D	00/00/00
		IT 1106623 B	11/11/85
		IT 7850601 D	00/00/00
		JP 54041881 A	03/04/79
		ZA 7804463 A	25/07/79

11-D